

**REMARKS****Summary and Status of Amendments**

In the present Amendment, claims 1, 2, 4-6, and 8 have been amended, and claim 10 has been canceled, with claim 1 being an independent claim. Claims 1-9 will remain pending and under consideration.

Applicants note that claim 1 has been amended to recite amongst other features, "for the mode of covalent bond." Support for the amendment may be found throughout Applicants' originally filed disclosure, such as at page 6, second paragraph, and page 10, last paragraph to page 11, second paragraph, in which examples of the procedure are disclosed. Claim 2 has been amended to remove "modifying" to recite "constructing." Support for the amendment may be found throughout Applicants' originally filed disclosure, such as at page 4, line 14, and page 7, line 18. Claim 4 has been amended to recite "determining correspondence of two dimensional graphs for the query molecule and the trial compound." Support for the amendment may be found throughout Applicants' originally filed disclosure, such as at page 11, line 20 to page 12, line 10. Claims 5-6 and 8 have been amended to be more in conformance with idiomatic English and standard PTO practice. No new matter is added.

Request for Continued Examination and allowance of the application are respectfully requested.

**Information Disclosure Statement**

Applicants express appreciation to the Examiner for acknowledgement of the Information Disclosure Statement filed May 23, 2005, by returning an initialed copy of the Form PTO-1449 submitted therein.

**Response to 35 U.S.C. § 101 Rejection**

Claims 1-10 are rejected under 35 U.S.C. § 101 because the claimed invention is allegedly directed to non-statutory subject matter and because the claimed invention allegedly lacks patentable utility. The Office Action asserts that the claims are directed to methods for obtaining data and selecting a compound, and claims that are so-directed are non-statutory because they are equivalent to mental processes. Further, the Office Action asserts that none of the methods recites any physical method step or any step of transforming data which would render the claims statutory.

In response, Applicants note that claim 1 has been amended to recite "for the mode of covalent bond." In addition to the arguments of record, Applicants note that the claims recite use of a "database" and that this term as used is a structural characteristic of the method. The claimed method is advantageously useful for selecting compounds from a "database" which may comprise many thousands of compounds. The specification specifically describes how such methods are advantageously employed for selecting lead-compound candidates for one or more databases. The claimed method does not merely consist of matching one query

compound with one candidate compound. The method involves, for example, matching a query compound with numerous compounds in a database and selecting a group of likely lead-compound candidates.

One of ordinary skill in the art has available a growing number of databases comprising a vast collection of compounds. However, the ordinary skilled artisan has limited tools available for mining the data contained in the vast compound databases. Applicants note that the ability to identify, compare, or select specific lead-compound candidates from an extensive database is a concrete and tangible result. Thus, the method achieves a specific concrete and useful purpose. The nature of how data is stored in such extensive databases makes it not easily reviewable and difficult to match and/or select lead-candidate compounds. Applicants' present invention is characterized in that it enables extremely rapid search for lead-candidate compounds because it does not require information about three-dimensional structure of compounds stored in a database and consideration of flexibility of conformation, binding scheme and the like. (See Specification page 19, last two paragraphs.) This capability and use of the claimed method also indicates that the method provides a concrete and tangible result.

Therefore, one of skill in the art would understand from reading the specification that the claimed method for selecting a lead-compound clearly produces a concrete, tangible, and useful result. For at least these reasons, Applicants submit that the claims are directed to statutory subject matter.

Accordingly, Applicants respectfully request that the rejection of claims 1-10 under 35 U.S.C. § 101 be withdrawn.

### **Response to 35 U.S.C. § 112 Rejections**

#### **Enablement Rejection**

Claims 1-10 are rejected under 35 U.S.C. § 112, first paragraph as failing to comply with the enablement requirement. The Office Action asserts that the claims are broadly directed to a lead-candidate compound capable of "interacting" with any type of biopolymer. Further, the Examiner alleges that the specification does not teach particular conditions which must be met to select a compound as a "lead-candidate." For instance, the Office Action asserts that the specification does not teach how to single out any particular compound as a "better" ligand than the others, or which binds more tightly than another. The Office Action also asserts that the claims are allegedly not enabled for selection of a lead-candidate compound which binds to any type of biopolymer because neither the specification nor alleged "prior art" (Desjarlais et al., J. Med. Chem. (1988) Vol. 31, pp. 722-729; and Nishibata et al., Tetrahedron (1991) Vol. 47, no. 43, pp. 8985-8990) teaches specific parameters for selection of a compound(s) which bind to any biopolymer. Applicants traverse this rejection for reasons of record, and as supplemented below.

However, solely to advance prosecution without expressing agreement or acquiescence with the rejection, Applicants have amended claim 1 to recite "for the

mode of covalent bond" to further clarify that the matching is made for the mode of covalent bond. Applicants note that the matching for the mode of covalent bond is enabled throughout the specification, such as at page 6, second paragraph, and page 10, last paragraph to page 11, second paragraph, in which examples of the procedure is disclosed.

In addition to Applicants' argument dated March 23, 2005, Applicants respectfully submit that the subject matter recited in the claims is enabled so that one of ordinary skill in the art would be capable of practicing Applicants' invention without undue experimentation. Applicants note that as admitted by the Examiner on page 5 of the Office Action, the specification is enabling for identifying compounds which may bind to proteins such as dihydrofolate reductase. Applicants note that it is within the scope of common technical knowledge of one of ordinary skill in the art following the guidance set forth in Applicants' specification, such as Example 1 and Fig. 3 of compounds which bind to dihydrofolate reductase, that other compounds may be identified which bind to biopolymers using the claimed method for selecting at least one lead-candidate compound capable of binding as a ligand to a biopolymer, from a compound database comprising information on atomic types and covalent bonds of compounds in the database, comprising selecting at least one trial compound by matching at least one query molecule capable of binding to the biopolymer with trial compounds stored in the database for the mode of covalent bond.

The Office's allegation that the instant specification teaches "'use" of similar

parameters" disclosed in Desjarlais et al. and Nishibata et al., but does not teach specific parameters that would allow one of skill in the art to know what to select (see page 7 of the Office Action), is not sufficient to support a lack of enablement.

Applicants' specification provides a detailed discussion of the state of the prior art, and a discussion of methods for searching for desired compounds from a database of three-dimensional structures along with guidance for matching query molecules capable of binding to a biopolymer with compounds stored in a database based on information about atomic types and mode of covalent bonds so that one having ordinary skill in the art can practice Applicants' invention without undue experimentation. For instance, the specification at page 2, lines 8-24 shows that "[w]hen information about three-dimensional structure of the biopolymer is not available, one can use structural information of drug molecules known to be capable of binding to the biopolymer and can use structural information of drug molecules known to be capable of binding to the biopolymer and can use criteria whether kinds and relative three-dimensional positions of functional groups correspond well between the compound and the drug molecules" was known to one of skill in the art at the time the invention was made. One of skill in the art would understand that the specification enables a variety of specific methodologies for obtaining lead-candidate compounds with an even higher possibility of binding as a ligand to the target biopolymer. For example, see page 15, second full paragraph of the specification. Also, as indicated by the Examiner on page 6 and 7 of the Office Action, the "instant specification teaches "use" of similar parameters

[technically known to one of ordinary skill in the art] (e.g. information about atomic types and mode of covalent bonding)" so that one of ordinary skill in the art would know the parameters, e.g., atomic types and mode of covalent bonds, by which to select the claimed lead-candidate compounds by matching at least one query molecule capable of binding to a biopolymer based on the information about atomic types and mode of covalent bonding.

In addition, pages 4-5, and 7-17 of the specification disclose selection of lead-candidate compounds by matching at least one query molecule capable of binding to the biopolymer with compounds stored in the database based on information regarding atomic types and covalent bond mode of the query molecules. The structures of the query compounds may be constructed by an automatic construction method by calculations based upon the three-dimensional structure information for the biopolymer and/or known ligands. The number of query molecules are reduced based on structural information as shown on page 17 of the specification using reduction criteria such as molecular skeletons, flexibility of molecules, and binding schemes to ligand binding sites. Additionally, when molecular structures are used as query molecules, criteria including intramolecular and intermolecular energy, energy of the whole system, number of hydrogen bonds, hydrogen bonds to specified locations, formation of ionic bonds, and number of rings may be used. It is common technical knowledge to one of ordinary skill in the art, and one of ordinary skill in the art can readily understand from the guidance set forth in the specification, that lead-candidate compounds may be

selected to bind to a biopolymer using the claimed method for selecting at least one lead-candidate compound capable of binding as a ligand to a biopolymer, from a compound database comprising information on atomic types and covalent bonds of compounds in the database, comprising selecting at least one trial compound by matching at least one query molecule capable of binding to the biopolymer with trial compounds stored in the database for the mode of covalent bond.

There would be no undue experimentation required to practice Applicants' disclosed and claimed invention. As the Court of Appeals for the Federal Circuit stated in In re Wands, 8 U.S.P.Q.2d 1400, 1404 (CAFC 1988):

Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. "the key word is 'undue,' not 'experimentation.'

The Wands factors to be considered in determining whether a disclosure would require undue experimentation are set forth in the Office Action have been summarized by the board in Ex parte Forman, 230 U.S.P.Q. at 547.

Weighing these factors under the present circumstances clearly demonstrates that the 35 U.S.C. 112, first paragraph, enablement rejection is improper and should be withdrawn. In this regard, (a) the quantity of experimentation would be low, (b) there is sufficient direction presented to make and use the claimed invention, (c) working examples are provided, and (d) the relative skill in the art, the nature of the invention, and the claim language are sufficiently related that undue experimentation would not be required to practice the disclosed and claimed invention. In this regard, sufficient guidance is provided for selecting at least one lead-

candidate compound capable of binding as a ligand to a biopolymer.

Furthermore, to the extent that the Office Action may be raising issues which interrelate utility and enablement, Applicants note that the Office has the initial burden of challenging an asserted utility, and the Office has failed to provide evidence showing that one of ordinary skill in the art would reasonably doubt the asserted utility. One of ordinary skill in the art would understand that molecules that bind a target biopolymer as a "ligand" are known to be useful as inhibitors or agonists of the biopolymer's native function. Therefore the utility of selecting compounds capable of binding as a ligand to the targeted biopolymer or protein is both credible and enabled by the instant disclosure.

Accordingly, the enablement rejection of claims 1-10 under 35 U.S.C. §112, first paragraph, should be withdrawn.

### **Written Description Rejection**

Claims 2 and 4 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. The Office Action asserts that claim 2 as amended to recite "modifying" is not supported by the originally filed disclosure or original claim 2, and is read to be broader than originally filed. The Office Action asserts that claim 4 recites the "algorithm of Ullman" but the specification allegedly does not set forth the actual algorithm anywhere nor incorporate by reference a publication describing the algorithm.

In response, and in order to advance prosecution and solely to more clearly describe the claimed subject matter, Applicants have amended claims 2 and 4. Applicants have amended claim 2 to replace “modifying” with “constructing.” Support for the amendment may be found throughout the specification, such as at page 4, line 14, and page 7, line 18. Claim 4 has been amended to recite “determining correspondence of two dimensional graphs for the query molecule and the trial compound,” which is a specific result achieved by the Ullman’s algorithm and well known to one of ordinary skill in the art at the time the present invention was made. Also, support for the amendment may be found throughout the specification, such as at page 11, line 20 to page 12, line 10.

Accordingly, the written description rejection of claims 2 and 4 under 35 U.S.C. § 112, first paragraph, should be withdrawn.

### **Indefiniteness Rejection**

Claims 1-10 are rejected under 35 U.S.C. §112, second paragraph, for indefiniteness. The Office Action asserts that claims 1-10 appear to be missing an element or nexus between the preamble and actual steps, thus the claims are allegedly indefinite. Claim 2 is asserted to be allegedly indefinite for failing to indicate what type of modification is intended by the term “modifying”. Claim 4 is allegedly indefinite because of the recitation “algorithm of Ullman.” of “the” algorithm of Ullman may be addressed by amendment to correct this informality if this phrase remains in the claim

as discussed above. Claim 6 is allegedly indefinite because of the recitation "step (a) to comprise steps (c) and (d); however no step (b) is recited." The Office Action asserts that the claims as amended do not recite any line indicators such as "(a)", "(b)", "(c)", etc. Similarly, claim 8 is allegedly indefinite because of the recitation "step (f) and/or a step (g)" and asserts that claim 3, from which claim 8 depends, recites only "a step (a)." Thus recitation of "steps (f) and (g), with no intervening steps, in claim 8 renders it unclear." The Office Action asserts that the claims as amended do not recite any line indicators such as "(a)", "(f)" or "(g)".

In response, Applicants respectfully submit that the claims pending prior to the present amendment definitely define what Applicants consider to be their invention. However, in order to advance prosecution of the present application, and without acquiescence, Applicants have amended claim 1 to recite "for the mode of covalent bond" to define that the matching is made for the mode of covalent bond. Support for the amendment may be found throughout the specification, such as at page 6, second paragraph, and page 10, last paragraph to page 11, second paragraph, in which examples of the procedure is disclosed.

Additionally, Applicants have amended claims 2 and 4 to even more clearly define features of the present invention. In particular, Applicants submit that the term "modifying" in claim 2 is definite because one skilled in the art would know what the term means in the context of the invention disclosed in the specification. In order to advance prosecution, and without acquiescence, Applicants have amended claim 2

removing “modifying” to recite “constructing.” Support for the amendment may be found throughout Applicants’ originally filed disclosure, such as at page 4, line 14, and page 7, line 18. Claim 4 has been amended to recite “determining correspondence of two dimensional graphs for the query molecule and the trial compound.” Applicants submit that it is common technical knowledge, and one of ordinary skill in the art would understand from reading the specification, such as at page 11, line 20 to page 12, line 10, that determining the correspondence of two dimensional graphs for the query molecule and the trial compound is a specific result achieved by the Ullman’s algorithm.

Furthermore, Applicants note that the Examiner appears to be attempting to read limitations or linkages into the claim where no such linkages exist. Applicants note that the active processes recited in claim 6 should be read as being further to those recited in claim 1, from which claim 6 depends. Also, claim 8 depends from claim 1 and therefore claim 8 should be read to include all the recitations of claim 1. Accordingly, the claims as presented are definite.

Accordingly, the indefiniteness rejection of claims 1-10 under 35 U.S.C. §112, second paragraph, should be withdrawn.

## CONCLUSION

In view of the foregoing reasons, the Examiner is respectfully requested to enter the amendment, reconsider and withdraw the rejection of record, and allow all pending claims.

Allowance of the application is requested, with an early mailing of the Notices of Allowance and Allowability.

If the Examiner has any questions, or wishes to discuss this matter, the Examiner is respectfully invited to contact the undersigned at the below-listed telephone number.

Respectfully submitted,  
A. ITAI et al.



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